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13. ABSTRACT ***(Maximum 200 Words)***

The purpose of this research is to investigate whether eating brown seaweed (*Undaria pinnatifida*) and soy powder can influence hormone levels that are thought to affect breast cancer risk. Brown seaweeds and soy foods are popular in Japan, where the incidence of breast cancer is about 1/6 the rate of that reported for American women. In several animal studies of diet and cancer, adding seaweed or soy to the normal diet resulted in longer healthy lives. Many studies have found that soy consumption in Asia appears to be linked directly to lower breast cancer risk, and laboratory studies have confirmed that soy reduces tumors in animal models. Constituents of soy have been proposed as antiestrogens and antioxidants, may induce apoptosis, and inhibit topoisomerase and angiogenesis (Zheng, 1999). We want to investigate how eating seaweed and soy together might affect hormone levels predictive of women's health. We will use commercially available seaweed and soy powder. These seaweeds and soy powder are commonly found in health food stores.

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INTRODUCTION:

The purpose of this research is to investigate whether eating brown seaweed (*Undaria pinnatifida*) and soy powder can influence hormone levels that are thought to affect breast cancer risk. Brown seaweeds and soy foods are popular in Japan, where the incidence of breast cancer is about 1/6 the rate of that reported for American women. In several animal studies of diet and cancer, adding seaweed or soy to the normal diet resulted in longer healthy lives. In several international studies, soy intake has been found associated with lower breast cancer risk. Many studies have found that soy consumption in Asia appears to be linked directly to lower breast cancer risk, and laboratory studies have confirmed that soy reduces tumors in animal models. Constituents of soy have been proposed as antiestrogens and antioxidants, may induce apoptosis, and inhibit topoisomerase and angiogenesis (Zheng, 1999). We want to investigate how eating seaweed and soy together might affect hormone levels predictive of women's health. We will use commercially available seaweed and soy powder. These seaweeds and soy powder are commonly found in health food stores.

BODY:

Task 1. Develop Plan for Study Computer Database, Months 1-3

a. **Normal study values will be entered for each outcome variable, so out-of range values will immediately alert investigators to potential problems.**
   Since all analyses are being performed at the end of the study, rather than concurrent with the study, and normal values may not be relevant, we are plotting the values longitudinally for each patient to see where an individual's values might have varied.

b. **Tracking system will be developed to monitor each volunteer, and to record data from laboratory analyses, medical histories, interviews, and diaries.**
   Tracking system is in place and is being used.

c. **Train project coordinator in patient-centered counseling to be used in this study.**
   Project coordinator was trained in patient-centered counseling.

d. **Orient the staff to the study, all of whom work in the Division of Population Studies, at the University of South Carolina.**
   Staff was oriented to the study, and understood the overall purpose and how it will be run.

Task 2. Seaweed, Months 1-3

a. **Identify exact location of seaweed to be used, visiting the collection site, overseeing drying, grinding, and encapsulation processes.**
   Seaweed samples were collected from Maine, Washington, Tasmania, British Columbia, Namibia, and commercially available samples were collected that originated in Iceland and Japan. All samples were analyzed for iodine content. Four seaweed harvesters were identified who could provide low iodine-containing brown seaweeds that are commonly eaten.

Each was visited to evaluate harvesting techniques, reliability of location identification, age of plants harvested, transportation methods, drying methods, and grinding facilities. One harvester (Mervyn Lee, Marine Resources, Hobart, Tasmania) was chosen, and seaweed has been ordered, to be delivered in encapsulated form.

b. Overseeing grinding and encapsulation of oatmeal for the control supplement.

Oatmeal, because of its mucopolysaccharide properties, was replaced by Maltodextrin, a more biochemically neutral placebo. The Maltodextrin was encapsulated by Beehive Botanicals, under the same conditions as the seaweed encapsulation. Both the seaweed and the placebo capsules are made of brown gelatin. The capsules were analyzed for iodine content, and found to have none.

c. Analysis of seaweed for iodine and seaweed and oatmeal for percentage of soluble and insoluble fiber.

We decided to rely on existing published fiber content analysis done on the *Undaria*, and the company analysis of Maltodextrin.

Task 3. Pilot Test, Months 4

a. Pilot test and refine data collection instruments.

1. Twenty-two commercially available seaweeds were analyzed for iodine content. The iodine content varied from 30 mcg/g to over 8,000 mcg/g. Since total iodine intake of more than 1,000 mcg/d is considered potentially toxic, the original choice of *Laminaria* (about 2,400 mcg/g) was changed to *Undaria* (about 51 mcg/g).
2. We did a preliminary study of two volunteers who took seaweed capsules with and without soy powder, to see if seaweed was likely to influence urinary phytoestrogen excretion. We found that seaweed alone made only minor differences, but seaweed plus soy made a 100-fold difference in the excretion of equol. Equol is thought to be the phytoestrogen of particular importance in breast cancer, and only about 1/3 to ½ of all Americans can produce equol. The synergism of seaweed (a fiber source) and soy seemed to make one of the volunteers become an equol producer. For the other woman was already an equol producer, and the addition of seaweed made no difference in equol excretion.
3. Based on this finding, we modified the pilot study to include 6 weeks of seaweed/placebo followed by a week of seaweed/placebo plus soy. We wrote a small grant to Protein Technologies and obtained high isoflavone soy powder for use in the study.
4. The Seven Day Dietary Recall Questionnaire was modified to include high phytoestrogen-containing vegetables.
5. Baseline, sleep, vegetable and fruit, menopausal symptoms, diet questionnaires and a daily journal were identified in the health literature, and modified to fit the requirements of this study.

6. Fabric bags were designed and sewn, for carrying the 6 liters of urine from home to the lab, and for storing at home during the collection periods.
7. Labeling system of color-coded and numbered sample collection vials was devised, and vials were labeled.
8. Randomized ID numbering system was devised, so that at each visit, the patients received new ID numbers. This was done to increase blindedness of sample analysis by laboratory personnel.
9.

Task 4. Subject Recruitment and Study, Months 5-10

No subjects have been recruited. I am awaiting Human Subjects approval.

Task 5. Data Analysis of Results from Healthy Volunteers, Months 11-12

No subjects have been recruited. I am awaiting Human Subjects approval.

a. Meetings with oncologists to present preliminary data.

Pending study IRB approval.

b. Final meeting with volunteers to explain study results and to answer any questions.

Pending study IRB approval.

c. Annual report to USARMC

Pending study IRB approval.

KEY RESEARCH ACCOMPLISHMENTS

I applied to transfer this grant from the University of Massachusetts to the University of South Carolina was made **December 1, 1999**. I was told that it would take between 6 to 8 weeks for the transfer of this approved project to my new institution. However, it was not until **June 30, 2000** that the grant was transferred to the Army IRB for review. After several months of revisions, and then negotiating between the lawyers of the University of South Carolina/Palmetto Health Alliance and the U.S. Army, everything seemed to be in order, and the final signatures were to be obtained. On **September 27, 2000**, I received the following message:

> Dear Dr. Teas,
> I looked them over and have sent them in to my Chair for review. It might be a few days as she has a board meeting today. I will keep you posted.
> Thanks.

However, on **October 3, 2000**, my file was transferred to a new Human Subjects Protection Specialist. I visited her in person **October 17, 2000**.

On **November 8, 2000,** I received a list of concerns, which I addressed.

On **December 7, 2000**, I received another list of concerns and another MFR concerning my grant. I addressed these concerns.

On **January 5, 2001**, I received another list of concerns from an unnamed nutritional consultant. These concerns have been addressed.

On **June 13, 2001**, my grant was deemed to need full Army IRB approval. In addition, there are further concerns and clarifications which either the original nutritionist or another unnamed nutritionist now require. My study has now been deemed to need full IRB approval, and it will be reviewed possibly on **July 23, 2001**.

REPORTABLE OUTCOMES

Poster was presented at the XVIIth International Seaweed Symposium, 28 January - 2 February 2001, Cape Town, South Africa.

CONCLUSIONS:

This study was approved by IRBs at the University of Massachusetts and the University of South Carolina/Palmetto Health Alliance. It has yet to be approved by the Army Human Protection Specialists, although the Army approved it 3 years ago.

It is hard to imagine the risks that millions of people in Japan daily experience as a result of eating seaweed and soy products, and even harder to understand how these perceived risks are consistent with the significantly lower breast cancer rates experienced by these people. The foods I am proposing to test are available in health food stores throughout the United States, and yet, the nutritionist associated with my project approval has decided that eating these foods constitutes greater than minimal risk.

I am at a loss to make any meaningful conclusions from this experience. It is possible that seaweed and soy are foreign foods, recently introduced to the US market, and that their Asian origins place them in a category of perceived American risk. It is easy to imagine that a similar project to test American hamburgers and french fries would be easily approved for a clinical test, not because they are healthier, but because Americans commonly eat them.

I also wonder how a proposal that was awarded based on scientific merit now needs each of the generally regarded as knowledge statements to be defined and further justified in a protocol that neither scientists nor subjects will ever see. I am curious about the usefulness of such a document to anyone other than the reviewers.

REFERENCES: None.

APPENDICES:

Poster (reduced in size) "Iodine in Dietary Seaweeds: Range of Values and Possible Concerns." XVIIth International Seaweed Symposium, 28 January - 2 February 2001, Cape Town, South Africa.

Iodine in Dietary Seaweeds: Range of Values and Possible Concerns

J. Teas[1], S. Pino[2], J. Cunningham[1], T. Hurley[1], A. Critchley[3], & L. Braverman[2]

[1]University of South Carolina, [2]Boston University, [3]University of Namibia [jane.teas@rmh.edu]

Is the iodine in seaweed biologically available to humans?

tudy:

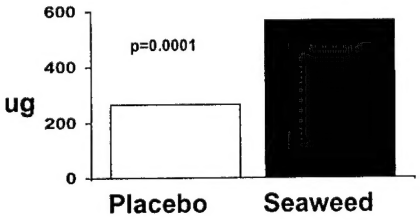
25 healthy postmenopausal white women (avg. age 58 years)

normal thyroid stimulating hormone (TSH) values

5 grams/day seaweed (*Alaria*, 550 ug iodine) or placebo

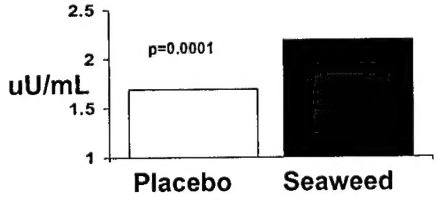
six week crossover study.

24 Hour Urinary Iodine



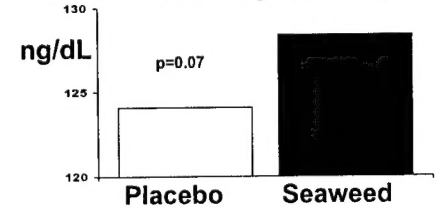
Although 550 ug supplemental iodine were given per day, only 300 ug of this was excreted.

Serum Thyroid Stimulating Hormone (TSH)



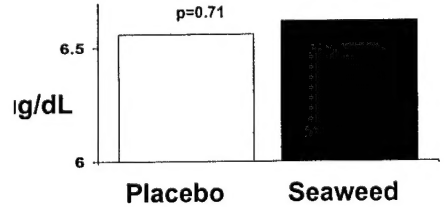
All within normal range (0.5 - 5.0 uU/mL)

Serum Triiodothyronine (T3)



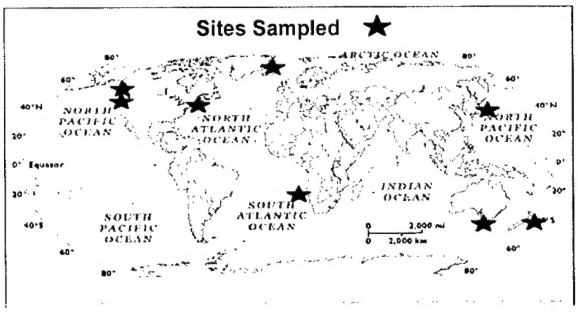
All within normal range (88-160 ng/dL)

Serum Thyroxine (T4)



All within normal range (5-12 ug/dL)

How much iodine is in seaweed?



Iodine Content of Some Commercially Available Seaweeds

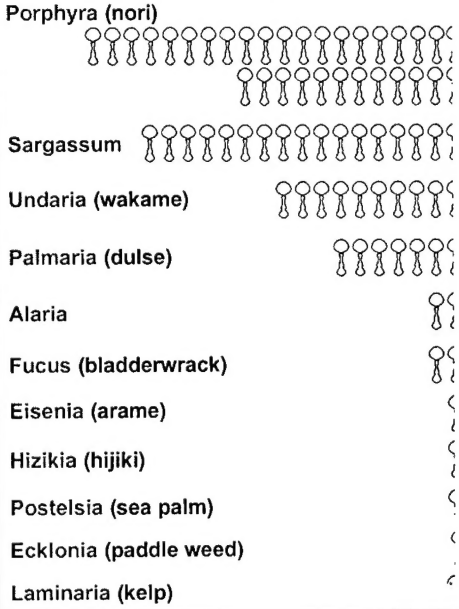
Name	Location	Form	N	Mean (SD) ug/g
Alaria esculenta				
alaria	Maine	whole	7	110 (30)
alaria	Maine	whole	5	431 (104)
Ascophyllum nodosum				
knotted wrack	Maine	whole	3	646 (392)
Eisenia bicyclis				
arame	Japan	whole	3	586 (56)
Ecklonia maxima				
paddle weed	Namibia	whole	6	2123 (352)
Fucus vesiculosis				
bladderwrack	Maine	whole	3	276 (82)
Hizikia fusiforme				
hijiki	Japan	whole	6	629 (153)
Laminaria				
L. longicurus	Maine	whole	3	746 (26)
" "	" "	" "	6	1862 (520)
L. saccharina	BC Canada	capsule	5	1259 (200)
" "	" "	" "	5	1513 (117)
kombu	Washington	whole	7	1350 (362)
wild kelp	Maine	whole	7	1356 (665)
L. digitata	Maine	whole	6	1997 (563)
" "	" "	" "	6	2984 (910)
" "	Iceland	granules	6	8165 (373)
L. angustata	Japan	powdered	4	2353 (65)
L. pallida	Namibia	whole	10	2761 (546)
Palmaria palmata				
dulse	Maine	whole	3	72 (23)
Porphyra tenera				
nori	Japan	sheet	3	16 (2)
Postelsia palmaeformis				
sea palm	California	whole	7	871 (231)
Sargassum muticum				
sargassum	Washington	whole	5	30 (1)
Undaria pinnatifada				
undaria spore	Tasmania	tablets	4	22 (1)
" "	" "	powder	5	53 (3)
undaria	" "	powder	5	32 (4)
" "	" "	whole	4	41 (14)
" "	New Zealand	whole	6	115 (42)
wakame	Japan	whole	6	42 (17)

Is iodine content the same in all parts of a seaweed?

Form	Stage	Part	N	Mean (SD) ug/g
Laminaria pallida (Namibia)				
sunbleached	adult	meristem	3	514 (42)
" "	" "	blade	3	1034 (92)
" "	" "	stipe	3	1452 (226)
sunbleached drift	adult	blade	3	1925 (502)
" "	" "	" "	3	1958 (251)
fresh	adult	stipe	3	2298 (524)
" "	" "	blade	3	3041 (702)
" "	" "	meristem	3	4260 (1314)
" "	" "	" "	3	4555 (1095)
" "	juvenile	<50 cm	3	6571 (715)
Ecklonia maxima (Namibia)				
fresh	adult	stipe	3	1071 (196)
" "	" "	" "	3	1340 (441)
" "	" "	" "	3	1355 (308)
" "	" "	blade	3	2500 (464)
" "	" "	" "	3	3139 (379)

How much seaweed equals the Maximum Tolerated Dose (1000 ug/day)?

(Assuming 2 grams of dried seaweed is about 1 teaspoon)



Mitigating Factors

- Bioavailability of iodine in different species of seaweed may vary.
- Concomitant intake of dietary goitrogens such as cruciferous vegetables, taro.
- Individual sensitivity.
- Habitual intake of seaweed versus occasional or never.
- In utero or childhood exposure to seaweed.
- Loss due to cooking methods.
- Hot weather--lost through sweat.
- Exercise--lost through sweat.
- Lactation--lost through breast milk.

Conclusions

- Levels of iodine vary by type, age, part and habitat of seaweed.
- Iodine found in *Alaria*, and possibly other seaweeds, is biologically available.
- Low-iodine seaweed can modify thyroid function.
- Very high levels of iodine in some common seaweeds may result in hyper- or hypo- thyroidism among sensitive individuals.

This work was sponsored by the Susan G. Komen Foundation, and by the US Army Medical Research and Materiel Command under DAMD 17-98-1-8207.